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REMARKS

Claims 66 and 70 have been amended. Claims 67-69 and 76-77 have been cancelled. Claims 78-82 have been added. Upon entry of the amendment, claims 66, 70-75, and 78-82 will be pending. Claims 78-82 find support throughout the application especially in Tables 2 and 3 and Example 3. Claims 66 and 72-74 are rejected under 35 USC 102 for allegedly being anticipated by Kole. Claims 66-75 are variously rejected for obviousness over Kole in view of various other references. The claims have been amended as set forth above. The Applicants submit that in view of the forgoing amendments and the following remarks, the application is now in proper form for allowance.

I. Rejection for anticipation under 102

Claims 66 and 72-74 are rejected under 35 USC 102(b) for allegedly being anticipated by Kole (USP 5,627,274). Claim 66 now includes the limitation that the oligonucleotide must include a 2'-O-methoxyethyl modification. On page 7 of the office action, the Examiner states that Kole does not teach 2'-O-methoxyethyl modifications. Therefore the rejection of claim 66 is overcome. As claims 72-74 are dependent on the non-anticipated claim 66, they are also not anticipated. Therefore, the rejection under 35 U.S.C. 102(b) is overcome.

The newly added claims 78-82 also include the limitation of a 2'-O-methoxyethyl modification. Therefore, they are not anticipated by Kole.

II. Rejection for obviousness under 103

Claims 66 and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kole as evidenced by Clark and Nyce. The Examiner states that Kole teaches a method of administering an antisense oligonucleotide into a lung of a patient as a therapeutic treatment of disease. The Examiner further states that Kole teaches 2'-O-methyl modifications that form stable hybrids with RNA that are not degraded by RNase H. The abstract of Kole states that the oligonucleotides are designed to modulate splicing; therefore, not to promote degradation of the transcript. The Examiner further states that Clark teaches the size of respirable particles and that

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Nyce teaches formulation of oligonucleotides for pulmonary delivery as liquids or solids, in water or as dry powders.

In the rejection, the Examiner does not indicate any teachings regarding the limitation of a 2'-O-methoxyethyl modification as now recited in claim 66. Therefore, claim 66 is not obvious in view of this combination of references. As the remaining claims in the rejection of this group of claims, claims 72-75, are dependent on the non-obvious claim 66, they are also not obvious in view of this rejection.

Claims 66-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kole in view of Nyce further in view of Nicklin. As discussed above, Kole teaches oligonucleotides to redirect splicing, not to degrade, target mRNAs. To achieve this mechanism of action, Kole includes specific oligonucleotide modifications. Nyce teaches oligonucleotides to promote degradation of the mRNA transcript targeted by an oligonucleotide, i.e., RNase H activity. See, for example page 16, lines 14-19. Nyce concludes that:

This result [reduction of adenosine receptor mRNA levels by 50% after oligonucleotide treatment] showed that HAdALAS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A₁ receptor, which is involved in asthma.

Similarly, Nicklin teaches oligonucleotides to promote RNase H cleavage. Nicklin teaches:

These oligonucleotides typically contain at least one region of modified nucleotides that confer one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for RNase H cleavage. (sentence bridging pages 2 and 3)

A list of 2' modifications are presented that increase the affinity of the oligonucleotide for the target. No discussion is provided regarding any alterations in nuclease resistance provided by such modifications. Later, at the end of the same paragraph Nicklin further teaches that:

A variety of oligonucleotide modifications have been demonstrated to enhance or confer nuclease resistance. Oligonucleotides which contain at least one phosphorothiate modification are presently more preferred. In some cases,

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oligonucleotide modifications which enhance target binding affinity are also, independently, able to enhance nuclease resistance.

In view of the teachings of Nicklin, one would assume that incorporation of phosphorothioate linkages would inhibit RNase H activity as they increase nuclease resistance. However, incorporation of phosphorothioate linkages into an oligonucleotide backbone does not inhibit RNase H.

Applicants submit that one making oligonucleotides that do not promote RNase H cleavage would not look to a reference that teaches oligonucleotides that promote RNase H cleavage to determine what chemical modifications to use. Therefore, the combination of references is not proper.

Moreover, Nicklin teaches a long series of 2'-modifications on page 4 as indicated by the Examiner. Applicants submit that there is no motivation to select the specific 2'-modification now claimed. The MPEP 2144.08(A)(4) states:

Office personnel should determine whether one of ordinary skill in the art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus. See, e.g., *Ochiai*, 71 F.3d at 1569-70, 37 USPQ2d at 1131; *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatenability requires that the teaching of the prior art suggest the *claimed compounds* to a person of ordinary skill in the art." (emphasis in the original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901; *In re Lahu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). See also *In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996) (discussing motivation to combine).

No motivation is provided to select the specific 2'-modification that is included in claims 66 and 78, the two independent claims pending in the case. This picking and choosing could only be achieved by the use of impermissible hindsight by the Examiner as there is no motivation in Nicklin to select that single modification from the 2'-modifications listed in the specification.

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Therefore, the rejection of claims 66-75 is improper and is overcome. Moreover, the newly added claims are not obvious in view of the prior art and also allowable.

FEES


The Applicants hereby authorize to Commissioner to charge Deposit Account 50-0252 referencing case number ISIS-3561 the fee for a Request for Continued Examination, small entity. It is believed that no further fee is due with this response. However, if an additional fee is due, the Commissioner is hereby authorized to charge the Deposit Account listed above referencing this case number.

CONCLUSIONS

In view of these amendments and remarks, the Applicants believe that the case is now in proper form for allowance. Prompt issuance of a Notice of Allowance is respectfully requested. If the Examiner believes that outstanding issues remain in the case, the Examiner is encouraged to call the undersigned Agent for Applicant listed below to discuss the matter.

Respectfully submitted,

Date: Aug 10, 2006


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